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#R CMD INSTALL \\Aa.ad.epa.gov\\ord\\RTP\\Users\\E-J\\jwambaug\\NETMyD~1\\Resear~1\\vLiverPBPK

library(vLiverPBPK)

#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for human for Acetochlor (published value):
Wetmore_Css(chem.CAS="34256-82-1")
#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for human for Acetochlor (calculated value):
calc_vLiver_Css(chem.CAS="34256-82-1")
#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for rat for Acetochlor (no published value, 0.5 quantile only):
Wetmore_Css(chem.CAS="34256-82-1",species="Rat")
#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for rat for Acetochlor (calculated value):
calc_vLiver_Css(chem.CAS="34256-82-1",species="Rat")
#Steady-state concentration (uM) for 1 mg/kg/day for 0.5 quantile for rat for Acetochlor (published value):
Wetmore_Css(chem.CAS="34256-82-1",species="Rat",which.quantile=0.5)
#Steady-state concentration (uM) for 1 mg/kg/day for 0.5 quantile for rat for Acetochlor (calculated value):
calc_vLiver_Css(chem.CAS="34256-82-1",species="Rat",which.quantile=0.5)
#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for mouse for Acetochlor (no published value, human and rat only):
Wetmore_Css(chem.CAS="34256-82-1",species="Mouse")
#Steady-state concentration (uM) for 1 mg/kg/day for 0.95 quantile for mouse for Acetochlor (calculated value):
calc_vLiver_Css(chem.CAS="34256-82-1",species="Mouse")

#State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for human, 0.95 quantile, for Acetochlor (published value):
Wetmore_Oral_Equiv(0.1,chem.CAS="34256-82-1")
#State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for human, 0.95 quantile, for Acetochlor (calculated value):
calc_vLiver_Oral_Equiv(0.1,chem.CAS="34256-82-1")
#State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for human, 0.05, 0.5, and 0.95 quantile, for Acetochlor (published values):
Wetmore_Oral_Equiv(0.1,chem.CAS="34256-82-1",which.quantile=c(0.05,0.5,0.95))
#State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for human, 0.05, 0.5, and 0.95 quantiles, for Acetochlor (calculated value):
calc_vLiver_Oral_Equiv(0.1,chem.CAS="34256-82-1",which.quantile=c(0.05,0.5,0.95))
#State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for rat, 0.95 quantile, for Acetochlor (calculated value):
calc_vLiver_Oral_Equiv(0.1,chem.CAS="34256-82-1",species="Rat")
#State-state oral equivalent dose (mg/kg BW/day) to produce 0.1 uM serum concentration for mouse, 0.95 quantile, for Acetochlor (calculated value):
calc_vLiver_Oral_Equiv(0.1,chem.CAS="34256-82-1",species="Mouse")

makeWetmoreCssPlot <-
function(Wetmore.human.values,pred.human.values,Wetmore.rat.values,pred.rat.values,chemlines=F,title="Recreation of SimCYP Results",xlim=c(10^-3,10^3),ylim=c(10^-3,10^3),log="xy",xlab="Css Predicted",ylab="Css Wetmore et al. (2012,2013)")
{
  plot(10^-6,10^-6,xlim=xlim,ylim=ylim,log=log,xlab=xlab,ylab=ylab)
}

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for (this.CAS in names(Wetmore.human.values))
{
  matplot(pred.human.values[[this.CAS]][1],Wetmore.human.values[[this.CAS]][1],pch=0,add=T)
  matplot(pred.human.values[[this.CAS]][2],Wetmore.human.values[[this.CAS]][2],pch=1,add=T)
  matplot(pred.human.values[[this.CAS]][3],Wetmore.human.values[[this.CAS]][3],pch=2,add=T)
  if (chemlines)
    matplot(c(pred.human.values[[this.CAS]][1],pred.human.values[[this.CAS]][2],pred.human.values[[this.CA
S]][3]),c(Wetmore.human.values[[this.CAS]][1],Wetmore.human.values[[this.CAS]][2],Wetmore.human.val
ues[[this.CAS]][3]),lty=3,add=T,type="l")
  }
  for (this.CAS in names(Wetmore.rat.values))
  {
    matplot(pred.rat.values[[this.CAS]][1],Wetmore.rat.values[[this.CAS]][1],pch=16,add=T)
  }
  matplot(c(10^-4,10^4),c(10^-4,10^4),lty=2,add=T,type="l")
  matplot(90,10^-1,pch=0,add=T)
  matplot(90,10^-1.25,pch=1,add=T)
  matplot(90,10^-1.5,pch=2,add=T)
  matplot(90,10^-1.75,pch=19,add=T)
  text(100,10^-1,"Lower 95th",pos=4)
  text(100,10^-1.25,"Median",pos=4)
  text(100,10^-1.5,"Upper 5th",pos=4)
  text(100,10^-1.75,"Rat",pos=4)
  title(title)
}

makeCssInfvsRDPlot <- function(inf.values,RD.values,set1.members,set1.label="Slow
Metabolism",set2.label="Rapid Metabolism",title="Comparison of Infusion and Repeated Dosing Steady
States",xlim=c(10^-3,10^3),ylim=c(10^-3,10^3),log="xy",xlab="Predicted Infusion Css",ylab="Predicted
Repeated Dosing Css")
{
  plot(10^-6,10^-6,xlim=xlim,ylim=ylim,log=log,xlab=xlab,ylab=ylab)
  for (this.CAS in names(inf.values[set1.members]))
  {
    matplot(inf.values[[this.CAS]][1],RD.values[[this.CAS]][1],pch=0,add=T)
  }
  for (this.CAS in names(inf.values[!set1.members]))
  {
    matplot(inf.values[[this.CAS]][1],RD.values[[this.CAS]][1],pch=15,add=T)
  }
  matplot(c(10^-4,10^4),c(10^-4,10^4),lty=2,add=T,type="l")
  matplot(5,10^-1,pch=0,add=T)
  matplot(5,10^-1.25,pch=15,add=T)
  text(6,10^-1,set1.label,pos=4)
  text(6,10^-1.25,set2.label,pos=4)
  title(title)
}

```

Fig 1 SimCYP vs. our predictions:

```

vary.params <- list(BW=0.2)
vary.params[["liver.volume.per.kgBW"]]<-0.2
vary.params[["QGFRc"]]<-0.2
vary.params[["Qhc"]]<-0.2
vary.params[["million.cells.per.gliver"]]<-0.2
vary.params[["CLint"]]<-0.2

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```

Wetmore.human.values <- NULL
vLiver.human.values <- NULL
for (this.CAS in get_Wetmore_CAS())
  if (this.CAS %in% get_Css_withlodplasma_CAS())
  {
    Wetmore.human.values[[this.CAS]] <-
      c(Wetmore_Css(chem.CAS=this.CAS,which.quantile=0.05),Wetmore_Css(chem.CAS=this.CAS,which.quantile=0.5),Wetmore_Css(chem.CAS=this.CAS,which.quantile=0.95))
    these.params <- parameterize_SteadyState(this.CAS)
    vLiver.human.values[[this.CAS]] <-
      UVPKM("calc_Css",these.params,CV.params=vary.params,which.quantile=c(0.05,0.5,0.95))
  }

vLiver.rat.values <- NULL
Wetmore.rat.values <- NULL
for (this.CAS in get_Wetmore_CAS("Rat"))
  if (this.CAS %in% get_Css_withlodplasma_CAS("Rat"))
  {
    Wetmore.rat.values[[this.CAS]] <-
      Wetmore_Css(chem.CAS=this.CAS,species="Rat",which.quantile=0.5)
    these.params <- parameterize_SteadyState(this.CAS,species="Rat")
    vLiver.rat.values[[this.CAS]] <- calc_Css(these.params)
  }

makeWetmoreCssPlot(Wetmore.human.values,vLiver.human.values,Wetmore.rat.values,vLiver.rat.values
,chemlines=T)

```

Fig 2 SimCYP vs. our predictions with censored Fub:

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censored.params<-list(fub=list(sd=0.2,lod=0.01))

Wetmore.fub.human.values <- NULL
vLiver.fub.human.values <- NULL
for (this.CAS in get_Wetmore_CAS())
  if (this.CAS %in% get_Css_CAS())
  {
    Wetmore.fub.human.values[[this.CAS]] <-
      c(Wetmore_Css(chem.CAS=this.CAS,which.quantile=0.05),Wetmore_Css(chem.CAS=this.CAS,which.quantile=0.5),Wetmore_Css(chem.CAS=this.CAS,which.quantile=0.95))
    these.params <- parameterize_SteadyState(this.CAS)
    vLiver.fub.human.values[[this.CAS]] <-
      UVPKM("calc_Css",these.params,CV.params=vary.params,censored.params=censored.params,which.quantile=c(0.05,0.5,0.95))
  }

Wetmore.fub.rat.values <- NULL
vLiver.fub.rat.values <- NULL
for (this.CAS in get_Wetmore_CAS("Rat"))
  if (this.CAS %in% get_Css_CAS("Rat"))
  {
    Wetmore.fub.rat.values[[this.CAS]] <-

```

```

Wetmore_Css(chem.CAS=this.CAS,which.quantile=0.5,species="Rat")
these.params <- parameterize_SteadyState(this.CAS,species="Rat")
vLiver.fub.rat.values[[this.CAS]] <-
UVPKM("calc_Css",these.params,censored.params=censored.params,which.quantile=0.5)
}

makeWetmoreCssPlot(Wetmore.fub.human.values,vLiver.fub.human.values,Wetmore.fub.rat.values,vLiver.fub.rat.values,title="Fub Left-Censored at Limit of Detection",chemlines=T)

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#Fig 3 Infusion Css vs. Daily dosing PBPK Css

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infusion.human.values <- NULL
dailydosing.human.values <- NULL
CLint.values <- NULL
for (this.CAS in get_PBPK_CAS())
  if (this.CAS %in% get_Css_CAS())
  {
    these.params <- parameterize_SteadyState(this.CAS)
    infusion.human.values[[this.CAS]] <- calc_Css(these.params)
    these.params <- parameterize_vLiverPBPK(this.CAS)
    dailydosing.human.values[[this.CAS]] <- calc_Css(these.params,doses.per.day=3)
    CLint.values[[this.CAS]] <-
chem.physical_and_invitro.data[chem.physical_and_invitro.data$CAS==this.CAS,"Human.Clint"]
  }

set1 <- as.numeric(unlist(CLint.values))>median(as.numeric(unlist(CLint.values)))
makeCssInfvsRDPlot(infusion.human.values,dailydosing.human.values,set1)

```